Models to Predict Hepatitis B Virus Infection Among Patients With Cancer Undergoing Systemic Anticancer Therapy: A Prospective Cohort Study

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ABSTRACT

Purpose

Most patients with cancer are not screened for hepatitis B virus (HBV) infection before undergoing anticancer therapy, and optimal screening strategies are unknown. We sought to develop selective HBV screening strategies for patients who require systemic anticancer therapy.

Methods

This prospective cohort study included adults age ≥ 18 years with solid or hematologic malignancies who received systemic anticancer therapy at a comprehensive cancer center during 2013 and 2014. Patients underwent hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody testing, and completed a 19-question modified Centers for Disease Control and Prevention (CDC) HBV survey. Multivariable models that predict chronic or past HBV infection were developed and validated using bootstrapping.

Results

A total of 2,124 patients (mean age, 58 ± 13 years) completed the risk survey and HBV testing. Of these, 54% were women; 77% were non-Hispanic white, 11% Hispanic, 8% black, and 4% Asian; and 20% had a hematologic malignancy and 80% a solid tumor. Almost 12% were born outside the United States. The prevalence was 0.3% for chronic HBV infection and 6% for past HBV infection. Significant predictors of positive hepatitis B surface antigen or hepatitis B core antibody tests were as follows: men who had sex with men, black or Asian race, birthplace outside the United States, parent's birthplace outside the United States, household exposure to HBV, age ≥ 50 years, and history of injection drug use. The area under the receiver operating characteristic curve of the model on the basis of these seven predictors was 0.79 (95% CI, 0.73 to 0.82). The modified CDC survey and brief tools with fewer than seven questions yielded similar false-negative rates (0% and 0% to 0.7%, respectively).

Conclusion

An internally validated risk tool performed as well as the modified CDC survey; however, more than 90% of patients who completed the tool would still require HBV testing. Universal HBV testing is more efficient than risk-based screening.

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INTRODUCTION

After immunosuppressive therapy, patients with hepatitis B virus (HBV) infection are at risk for reactivation of the HBV infection, which can lead to a flare of hepatitis with the associated risks of liver failure and death.¹⁻⁵ Identification of patients with HBV infection at the onset of anticancer therapy is crucial to prevent HBV reactivation; however, despite the existence of well-established

risk factors for HBV infection⁶ on the basis of demographics, sexual and lifestyle behaviors, and medical conditions, risk factors are seldom assessed because of time constraints. Recommendations to identify patients with HBV infection before anticancer therapy have varied from universal serologic testing to limited testing in populations that are at risk.^{1-4,7} At present, there is no consensus on how to accurately and efficiently identify persons who are at risk, which has resulted in suboptimal HBV testing among

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patients with cancer who are anticipated to receive anticancer therapy^{8,9} as well as preventable adverse liver outcomes.¹⁰ We sought to develop, validate, and compare selective HBV screening strategies on the basis of predictors of HBV infection for patients who require systemic anticancer therapy.

METHODS

We conducted a prospective, observational study of adults age ≥ 18 years with cancer who presented for their first outpatient systemic anticancer therapy appointment at The University of Texas MD Anderson Cancer Center from July 2013 through December 2014. Patients who were previously found to have positive hepatitis B surface antigen (HBsAg) or total immunoglobulin hepatitis B core antibody (anti-HBc) test results more than 3 months before their first outpatient anticancer therapy appointment were excluded, as were patients who were taking any of the following anti-HBV medications: adefovir, entecavir, interferon, lamivudine, telbivudine, or tenofovir disoproxil fumarate. Because of the high volume of eligible patients and logistical challenges of approaching patients receiving cancer therapy in three centers in two buildings, after the first 3 months of our study, we used a simple random sampling algorithm to identify 80% of eligible patients who received cancer therapy during an 11-hour period each weekday. We assessed the age, gender, race, and ethnicity of eligible patients who did not enroll. All patients provided written informed consent. This study was approved by the institutional review board of The University of Texas MD Anderson Cancer Center before data collection.

Participants completed a survey of HBV risk factors from a publicly available Centers for Disease Control and Prevention (CDC) hepatitis risk assessment¹¹ that was consistent with national recommendations.^{1,6} The CDC hepatitis risk assessment included 18 questions about age and gender; place of birth; blood transfusion or organ transplantation before 1992 or clotting factor disorder; history of chronic liver disease, HIV or AIDS, or diabetes; sexual behaviors; injection drug use; household exposure to HBV infection; and other factors. We added a question about race and ethnicity for a total of 19 questions in our survey, hereafter referred to as the modified CDC survey. Patients self-reported their type of cancer.

Participants had the following HBV serologic tests performed within 3 months before or 2 months after study enrollment: HBsAg, total anti-HBc, and hepatitis B surface antibody (anti-HBs quantitative assay). Positive HBsAg and anti-HBc test results indicated chronic HBV infection. Negative HBsAg and positive anti-HBc test results, regardless of anti-HBs result, indicated past HBV infection. Positive anti-HBs test results indicated immunity from past HBV infection (in patients with positive anti-HBc results) or previous immunization (in patients with negative anti-HBc results). Per study protocol, patients with chronic or past HBV infection and hematologic malignancies were started on antiviral prophylaxis. Per usual care, patients with positive HBsAg or anti-HBc test results had HBV DNA tests performed using the COBAS AmpliPrep/COBAS TaqMan HBV test (version 2.0; Roche Molecular Systems, Pleasanton, CA).

Fisher's exact and χ^2 tests¹² were used to compare patient characteristics by HBV infection status in univariable analyses. The initial multivariable logistic regression model was obtained by including an initial set of candidate predictor variables with P values $< .20$ from the univariable analysis. Clinical predictors of chronic or past HBV infection were chosen using stepwise backward elimination in which the P value required for a variable to enter the model was .10, and the P value for a variable to be retained in the model was .05. The goodness of fit of a selected model was assessed using the Hosmer-Lemeshow χ^2 test. The discriminative capacity of the model was evaluated via receiver operating characteristic curve analysis and measured by the area under the receiver operating characteristic curve (AUC). Only patients who completed all questions were included in the modeling—complete-case analysis. To obtain reliable parameter estimates, we recoded gender into three groups as follows: female, men having sex with men, and men not having sex with men.

To address the issue of overfitting from using the same data set for fitting and predicting, we used bootstrapping,¹³ a data-based simulation method for statistical inference, with 500 bootstrap samples with replacement to obtain a bias-corrected estimate of the true AUC along with CIs.¹⁴ We also obtained the top five models by running stepwise logistic regressions independently on each bootstrap sample. From these top five models, we selected the model that we considered to be best on the basis of the highest AUC results of bootstrapping and clinical relevance. Screening strategies that had at least one affirmative answer to one of the predictors in the selected strategy or a subset of these predictors were compared with strategies that had at least one affirmative answer to an item on the modified CDC survey in terms of sensitivity and false-negative rate (FNR). To reduce the risk of HBV reactivation, we selected strategies with subsets of predictors with a low FNR.

RESULTS

A total of 4,131 patients were eligible. With the implementation of random sampling after month 3, we approached a total of 3,534 patients and enrolled 2,206 (62.4% of those approached and 53.4% of eligible patients). Of those enrolled (Fig 1), 67 patients did not complete serologic HBV testing, six did not complete the modified CDC survey, and nine withdrew, which left 2,124 patients in our final cohort. There was no difference in age ($P = .57$) or gender ($P = .48$) between our study cohort and nonenrollees; however, the proportions of black and Hispanic patients were lower in our study cohort—7.5% and 10.3%, respectively—than among nonenrollees—12.2% and 14.6%, respectively—and the proportions of Asian and non-Hispanic white patients were higher in our study cohort—3.2% and 77.1%, respectively—than among nonenrollees—0.5% and 63%, respectively (overall $P < .001$).

The mean ($\pm$ standard deviation) age of the 2,124 patients in our final study cohort was 58 years (± 13 years), and 54% of the patients were women (Table 1). Approximately 77% of the patients were non-Hispanic white, 11% Hispanic, 8% black, and 4% Asian. Of the 2,124 patients, 424 (20%) had a hematologic malignancy, 23 (1%) had hepatocellular cancer (HCC), and 1,677 (79%) had a non-HCC solid tumor.

The final study cohort included 135 patients with chronic (seven patients; 0.3%) or past (128 patients; 6%) HBV infection (Fig 1). Of the 128 patients with past HBV infection, 98 (77%) had evidence of resolved HBV infection (positive anti-HBc and anti-HBs test results), 27 (21%) had occult HBV infection (positive anti-HBc and negative anti-HBs test results), and three patients had indeterminate anti-HBs results that indicated a detectable antibody level that was below the threshold of quantification. Three hundred forty patients (17%) had only positive anti-HBs test results, which indicated previous immunization. At the onset of anticancer therapy, median HBV DNA level for patients with chronic HBV infection was 594.5 IU/mL (range, 26 to 3180 IU/mL), and none of the 104 patients with past HBV infection who underwent HBV DNA testing had detectable HBV DNA in serum. Among 1,677 patients with non-HCC solid tumors, four (0.2%) had chronic HBV infection and 99 (5.9%) had past HBV infection. Among the 23 patients with HCC, one had chronic HBV infection and one had past HBV infection. Among the 424 patients with hematologic malignancies, two (0.5%) had chronic HBV infection and 28 (6.6%) had past HBV infection.

Fig 1. Study flowchart. anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; (*) 80% random sampling implemented after month 3.

We examined HBV infection status according to patient characteristics as assessed in the modified CDC survey (Table 1). Rates of chronic or past HBV infection in various subgroups were as follows: 31% in Asian patients and nearly 16% in black patients versus 4.6% in white patients; 7.5% in men versus 5.4% in women; nearly 18% in patients who were born outside the United States and approximately 15% in patients with a parent who was born outside the United States versus less than 5% in patients who were born in the United States and patients with a parent who was born in the United States; almost 16% in patients with a household exposure to HBV infection versus approximately 6% in patients without such a household exposure; and more than 42% in men having sex with men and nearly 28% in patients who ever used injected drugs versus 6% in patients without these behaviors (6% for each group). Mean age was higher among patients with HBV infection than among those without HBV infection (61 ± 11.5 years ν 58 ± 13.3 years).

The initial multivariable model that predicted chronic or past HBV infection (Table 2) included seven significant predictors: age 50 to < 65 years or age $\geq$ 65 years, men having sex with men, black or Asian race, birthplace outside the United States, parent's

birthplace outside the United States, household exposure to HBV infection, and history of injection drug use. The bias-corrected AUC for this initial seven-question predictive model was 0.79 (95% CI, 0.73 to 0.82). Using the same bootstrap samples, we identified the five most frequently chosen models from bootstrapping methods (Table 3). Hosmer-Lemeshow goodness-of-fit tests indicated that all five models fitted the data well ($P > .15$). From these, we selected model C, which had seven questions, including patient's birthplace and parent's birthplace.

We next compared the performance of our 19-question modified CDC survey, the 18-question CDC hepatitis risk assessment, model C (Table 3), and models that contained seven, six, and five questions on the basis of the questions in model C predicting chronic or past HBV infection (Table 4). FNR for the modified CDC survey was 0%—in other words, all patients with chronic or past HBV infection would have been identified if we had serologically tested all patients with at least one affirmative answer to any of the survey's 19 questions. FNR for the CDC hepatitis risk assessment was 3%; use of this model to screen our cohort would have caused us to miss four patients with HBV infection, all of whom had

Table 1. HBV Status According to Cancer Type and Responses to the Modified 19-Question Centers for Disease Control and Prevention HBV Survey

Question	Answer	Total (N = 2,124)	HBV Status		Type of HBV Infection	
			Chronic or past HBV (n = 135)	No HBV (n = 1,989)	Chronic HBV (n = 7)	Past HBV (n = 128)
What is your age?	Mean (SD)	58 (13.3)	61 (11.5)	58 (13.3)	50 (10.5)	62 (11.3)
	< 50 years	508 (23.9)	22 (4.3)	486 (95.7)	3 (0.6)	19 (3.7)
	50 to < 65 years	881 (41.5)	58 (6.6)	823 (93.4)	3 (0.3)	55 (6.2)
What is your gender?	≥ 65 years	735 (34.6)	55 (7.5)	680 (92.5)	1 (0.1)	54 (7.3)
	Female	1,139 (53.6)	61 (5.4)	1,078 (94.6)	4 (0.4)	57 (5.0)
	Male	985 (46.4)	74 (7.5)	911 (92.5)	3 (0.3)	71 (7.2)
What is your race/ethnicity?†	Asian	85 (4.0)	26 (30.6)	59 (69.4)	4 (4.7)	22 (25.9)
	Black	165 (7.8)	26 (15.8)	139 (84.2)	0 (0.0)	26 (15.8)
	Hispanic	233 (11.0)	8 (3.4)	225 (96.6)	0 (0.0)	8 (3.4)
Were you born outside of the United States?	Non-Hispanic white	1,641 (77.3)	75 (4.6)	1,566 (95.4)	3 (0.2)	72 (4.4)
	Yes	252 (11.9)	45 (17.9)	207 (82.1)	6 (2.4)	39 (15.5)
	No	1,872 (88.1)	90 (4.8)	1,782 (95.2)	1 (0.1)	89 (4.8)
Was your mother born outside of the United States?	Yes	331 (15.6)	51 (15.4)	280 (84.6)	7 (2.1)	44 (13.3)
	No	1,788 (84.2)	83 (4.6)	1,705 (95.4)	0 (0.0)	83 (4.6)
Was your father born outside of the United States?	Yes	320 (15.1)	47 (14.7)	273 (85.3)	7 (2.2)	40 (12.5)
	No	1,797 (84.6)	88 (4.9)	1,709 (95.1)	0 (0.0)	88 (4.9)
Have you received a blood transfusion or organ transplantation before July 1992?	Yes	125 (5.9)	11 (8.8)	114 (91.2)	0 (0.0)	11 (8.8)
	No	1,999 (94.1)	124 (6.2)	1,875 (93.8)	7 (0.4)	117 (5.9)
Have you received a clotting factor concentrate before 1987?	Yes	12 (0.6)	0 (0.0)	12 (100.0)	0 (0.0)	0 (0.0)
	No	2,112 (99.4)	135 (6.4)	1,977 (93.6)	7 (0.3)	128 (6.1)
Have you been diagnosed with a clotting factor disorder?	Yes	50 (2.4)	1 (2.0)	49 (98.0)	0 (0.0)	1 (2.0)
	No	2,074 (97.6)	134 (6.5)	1,940 (93.5)	7 (0.3)	127 (6.1)
Have you been diagnosed with a chronic liver disease?	Yes	42 (2.0)	9 (21.4)	33 (78.6)	1 (2.4)	8 (19.0)
	No	2,082 (98.0)	126 (6.1)	1,956 (93.9)	6 (0.3)	120 (5.8)
Have you been diagnosed with HIV or AIDS?	Yes	3 (0.1)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)
	No	2,119 (99.8)	135 (6.4)	1,984 (93.6)	7 (0.3)	128 (6.0)
Have you been diagnosed with diabetes?	Yes	275 (12.9)	25 (9.1)	250 (90.9)	0 (0.0)	25 (9.1)
	No	1,849 (87.1)	110 (5.9)	1,739 (94.1)	7 (0.4)	103 (5.6)
Have you had more than one sexual partner in the past 6 months?	Yes	29 (1.4)	3 (10.3)	26 (89.7)	1 (3.4)	2 (6.9)
	No	2,087 (98.3)	132 (6.3)	1,955 (93.7)	6 (0.3)	126 (6.0)
Have you been diagnosed with a sexually transmitted disease in the last 6 months?	Yes	15 (0.7)	2 (13.3)	13 (86.7)	0 (0.0)	2 (13.3)
	No	2,109 (99.3)	133 (6.3)	1,976 (93.7)	7 (0.3)	126 (6.0)
Are you a woman who is currently pregnant?	Yes	2 (0.1)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
	No	2,122 (99.9)	135 (6.4)	1,987 (93.6)	7 (0.3)	128 (6.0)
Are you a man who is currently having sex with another man?	Yes	7 (0.3)	3 (42.9)	4 (57.1)	0 (0.0)	3 (42.9)
	No	2,117 (99.7)	132 (6.2)	1,985 (93.8)	7 (0.3)	125 (5.9)
Have you ever injected drugs, even if just once?	Yes	43 (2.0)	12 (27.9)	31 (72.1)	0 (0.0)	12 (27.9)
	No	2,081 (98.0)	123 (5.9)	1,958 (94.1)	7 (0.3)	116 (5.6)
Do you currently inject drugs?	Yes	4 (0.2)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)
	No	2,120 (99.8)	135 (6.4)	1,985 (93.6)	7 (0.3)	128 (6.0)
Have you ever lived with someone who has been diagnosed with HBV?	Yes	121 (5.7)	19 (15.7)	102 (84.3)	1 (0.8)	18 (14.9)
	No	2,003 (94.3)	116 (5.8)	1,887 (94.2)	6 (0.3)	110 (5.5)
Primary cancer type?	HCC	23 (1.1)	2 (8.7)	21 (91.3)	1 (4.4)	1 (4.4)
	Heme cancer	424 (20.0)	30 (7.1)	394 (92.9)	2 (0.5)	28 (6.6)
	Solid	1,677 (79.0)	103 (6.1)	1,574 (93.9)	4 (0.2)	99 (5.9)

NOTE: Data are given as No. (%) unless otherwise noted. Chronic HBV is indicated by hepatitis B surface antigen (HBsAg) positive/hepatitis B core antibody (anti-HBc) positive. Past HBV is indicated by HBsAg negative/anti-HBc positive with either hepatitis B surface antibody (anti-HBs) positive or anti-HBs negative. Percentages may not add up to 100% as a result of missing values. Number of missing values: "Was your mother born outside of the United States"—five patients; "Was your father born outside of the United States"—seven patients; "Have you been diagnosed with HIV or AIDS"—two patients; and "Have you had more than one sexual partner in the past 6 months"—eight patients. *P* values were obtained from Fisher's exact test unless otherwise stated.

Abbreviation: HBV, hepatitis B virus; SD, standard deviation.

**P* value from two independent sample *t* test.

†*P* value from χ^2 test.

‡All questions from the CDC hepatitis risk tool,¹¹ with the exception of the race and ethnicity item.

Table 2. Initial Multivariable Model Predicting Chronic or Past HBV Infection

Characteristic	Coefficient	Chronic or Past HBV Infection Odds Ratio (95% CI) (N = 2,120)*	P
Intercept	−4.33		
Age, years			
< 50	Ref	Ref	
50 to < 65	0.64	1.9 (1.1 to 3.3)	.02
≥ 65	0.98	2.7 (1.5 to 4.7)	< .01
Gender/sexual behaviors			
Female	Ref	Ref	
Male, MSM	3.31	27.5 (5.6 to 135.6)	< .01
Male, not MSM	0.34	1.4 (0.96 to 2.1)	.08
Race and ethnicity			
Non-Hispanic white	Ref	Ref	
Asian	1.14	3.1 (1.6 to 6.2)	< .01
Black	1.68	5.3 (3.2 to 8.9)	< .01
Hispanic	−0.64	0.53 (0.24 to 1.2)	.11
Birthplace outside the United States			
No	Ref	Ref	
Yes	0.88	2.4 (1.1 to 5.2)	.02
Parent's birthplace outside the United States			
No	Ref	Ref	
Yes	0.80	2.2 (1.1 to 4.7)	.03
History of injection drug use			
No	Ref	Ref	
Yes	2.32	10.2 (4.8 to 21.6)	< .01
Lived with someone with HBV infection			
No	Ref	Ref	
Yes	0.81	2.2 (1.3 to 4.0)	< .01

Abbreviations: HBV, hepatitis B virus; MSM, men having sex with men; Ref, reference.

*Four patients were excluded from the analysis as a result of a missing response in at least one of the predictors.

past HBV infection. Model C, which included male gender by history of sex with men, had an FNR of 1.5% and would have resulted in our missing two patients with past HBV infection. We then explored a seven-question model that was identical to model C, except that the question about sexual behaviors was omitted, and found that the FNR was 0%. A briefer six-question HBV screening model performed as well as the modified CDC survey, with an FNR of 0%. Omission of a potentially embarrassing question about injection drug use yielded our five-question HBV screening model, which had an FNR of 0.7% and would have missed one patient with past HBV infection (Table 4).

The proportion of patients who responded “Yes” to at least one survey question was 91% (1,932 of 2,124 patients) for the CDC hepatitis risk assessment, 92% (1,956 of 2,124 patients) for the modified CDC survey, 90% (1,908 of 2,124 patients) for our five-question survey, and 90% (1,910 of 2,124 patients) for our six-question survey. In other words, with the use of any of these surveys, approximately 90% of patients would require HBV serologic testing to achieve an FNR < 1%.

DISCUSSION

Identification of patients with HBV infection is the first step in preventing HBV reactivation as a result of anticancer therapies. In

this study, we found that HBV risk surveys with five or six questions performed as well as a 19-question modified CDC survey. Our brief surveys demonstrated excellent sensitivity and low FNRs, which indicated that they could be practicable tools with which to identify patients with cancer with HBV infection. To our knowledge, our study is the first to develop an HBV screening tool on the basis of HBV risk factors in a population of patients with cancer. Our study is also unique in employing bootstrapping to validate an initial predictive model and offering selective screening strategies for consideration. Only one previous study identified predictors of HBV infection—male gender and birthplace in an HBV-endemic country—and this was in individuals without cancer.¹⁵

Currently, there are no clear guidelines for HBV serologic testing in patients with cancer. Several approaches have been recommended—testing all patients, testing only those with risk factors for HBV infection, or testing only patients who would be treated with anticancer therapies associated with a high risk of HBV reactivation (eg, anti-CD20 monoclonal antibodies or stem cell transplantation).^{1,3-5} At present, HBV testing among patients with cancer remains suboptimal, and preventable adverse clinical outcomes continue to occur.

Each of the HBV identification methods that have been proposed to date has benefits and limitations. Universal HBV testing would identify all patients who are at risk for reactivation and would obviate questioning about HBV risk factors; however, universal serologic testing may not be cost effective in countries with a low prevalence of HBV infection, such as in the United States,¹⁶ and would have limited benefit among patients with solid tumors, whose risk of reactivation from cancer treatment might be low.^{17,18} HBV screening can be based on the therapy-related risk of HBV reactivation; however, many cancer therapies can cause HBV reactivation, and we do not have data by which to discern the risks of HBV reactivation associated with all cancers therapies. Furthermore, most patients receive a combination of anticancer drugs, and when one regimen fails, other regimens are used. Thus, screening only patients who will receive therapies associated with a high risk of HBV reactivation, such as anti-CD20 therapy, might expose some patients to the risk of HBV reactivation.

In this study, we developed HBV screening tools using data from patients who were treated at our tertiary comprehensive cancer center. Most patients at our center have commercial insurance or Medicare, and our previous studies have found a low prevalence of chronic HBV infection in our patients,^{8,19} which makes our institution an ideal setting in which to develop brief HBV screening tools.

For our six-question HBV screening tool, with questions about age, gender, race and ethnicity, birthplace, household exposure to HBV infection, and injection drug use, the sensitivity was 100%, and the FNR was 0%. Eliminating the question about injection drug use, which is potentially embarrassing and might not be answered honestly, resulted in a modest decrease in sensitivity, to 99.3%, and a modest increase in FNR, to 0.7%. This five-question model is brief and effective; thus, it may be suitable for geographic areas of low HBV infection prevalence. Moreover, this model could be incorporated into electronic medical records to increase HBV testing rates.^{20,21} In contrast, in areas where HBV infection is endemic, screening tools are likely not necessary and universal HBV testing—resources permitting—may be advisable.

Table 3. Top Five Models Predicting Chronic or Past HBV Infection Using Bootstrapping Methods of Validation

Characteristic	Model A			Model B			Model C*			Model D			Model E		
	OR (95% CI) (N = 2,124)	P		OR (95% CI) (N = 2,124)	P		OR (95% CI) (n = 2,120)†	P		OR (95% CI) (n = 2,120)†	P		OR (95% CI) (n = 2,120)†	P	
Age, years															
< 50	Ref			Ref			Ref			Ref			Ref		
50 to < 65	1.8 (1.1 to 3.1)	.03		1.8 (1.0 to 3.0)	.04		1.9 (1.1 to 3.3)	.02		1.9 (1.1 to 3.3)	.02		1.8 (1.1 to 3.2)	.03	
≥ 65	2.7 (1.5 to 4.6)	< .01		2.6 (1.5 to 4.5)	< .01		2.7 (1.5 to 4.7)	< .01		2.6 (1.5 to 4.5)	< .01		2.5 (1.4 to 4.4)	< .01	
Gender/sexual behaviors															
Female	Ref			Ref			Ref			Ref			Ref		
Male, MSM	25.9 (5.3 to 127.4)	< .01		26.2 (5.4 to 128.5)	< .01		27.5 (5.6 to 135.6)	< .01		27.2 (5.5 to 134.1)	< .01		27.6 (5.6 to 135.6)	< .01	
Male, not MSM	1.4 (0.95 to 2.0)	.09		1.4 (0.94 to 2.0)	.10		1.4 (0.96 to 2.1)	.08		1.4 (0.96 to 2.1)	.08		1.4 (0.96 to 2.1)	.08	
Race and ethnicity															
Non-Hispanic white	Ref			Ref			Ref			Ref			Ref		
Asian	3.6 (1.8 to 7.1)	< .01		3.6 (1.8 to 7.1)	< .01		3.1 (1.6 to 6.2)	< .01		4.0 (2.0 to 7.7)	< .01		3.9 (2.0 to 7.6)	< .01	
Black or African American	5.1 (3.1 to 8.4)	< .01		4.9 (3.0 to 8.2)	< .01		5.3 (3.2 to 8.9)	< .01		5.5 (3.3 to 9.1)	< .01		5.4 (3.3 to 9.0)	< .01	
Hispanic	0.63 (0.29 to 1.4)	.24		0.64 (0.30 to 1.4)	.25		0.53 (0.24 to 1.2)	.11		0.51 (0.23 to 1.1)	.10		0.52 (0.24 to 1.2)	.11	
Birthplace outside the United States															
No	Ref			Ref			Ref			Ref			Ref		
Yes	4.5 (2.6 to 7.8)	< .01		4.5 (2.6 to 7.7)	< .01		2.4 (1.1 to 5.2)	.02							
Parent's birthplace outside the United States															
No	Ref			Ref			Ref			Ref			Ref		
Yes							2.2 (1.1 to 4.7)	.03		3.9 (2.3 to 6.4)	< .01		3.8 (2.3 to 6.4)	< .01	
History of chronic liver disease															
No	Ref			Ref			Ref			Ref			Ref		
Yes															
History of injection drug use															
No	Ref			Ref			Ref			Ref			Ref		
Yes	10.2 (4.8 to 21.6)	< .01		8.8 (4.0 to 19.2)	< .01		10.2 (4.8 to 21.6)	< .01		9.5 (4.5 to 20.2)	< .01		8.0 (3.6 to 17.6)	< .01	
Lived with someone with HBV infection															
No	Ref			Ref			Ref			Ref			Ref		
Yes	2.3 (1.3 to 4.0)	< .01		2.2 (1.2 to 3.9)	< .01		2.2 (1.3 to 4.0)	< .01		2.2 (1.3 to 4.0)	< .01		2.2 (1.2 to 3.9)	< .01	
AUC	0.794 (0.748 to 0.827)			0.796 (0.734 to 0.825)			0.792 (0.73 to 0.822)			0.794 (0.748 to 0.828)			0.797 (0.722 to 0.827)		
No. of times model was chosen	56			39			37			35			31		

Abbreviations: AUC, area under the receiver operating characteristic curve; anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MSM, men having sex with men; OR, odds ratio; Ref, reference.

*This model was considered the best of the five models on the basis of the results of bootstrapping and clinical relevance.

†Four patients were excluded because of a missing response in at least one of the predictors.

Table 4. Comparison of Selective HBV Screening Strategies

Variable	18-Question CDC Hepatitis Risk Assessment	19-Question Modified CDC HBV Survey	Model C	7-Question Model	6-Question Model	5-Question Model
HBV risk factors	CDC ¹¹	CDC ¹¹ and race/ethnicity item	Age ≥ 50 years Asian or black race Birthplace outside the United States HBV household contact MSM Injection drug use Parent's birthplace outside the United States	Age ≥ 50 years Asian or black race Birthplace outside the United States HBV household contact Male Injection drug use Parent's birthplace outside the United States	Age ≥ 50 years Asian or black race Birthplace outside the United States HBV household contact Male Injection drug use	Age ≥ 50 years Asian or black race Birthplace outside US HBV household contact Male
Response to risk factors	Response	Response	Response	Response	Response	Response
HBV test result	HBV test result	HBV test result	HBV test result	HBV test result	HBV test result	HBV test result
Yes	Yes	Yes	Yes	Yes	Yes	Yes
No	No	No	No	No	No	No
Total	Total	Total	Total	Total	Total	Total
Sensitivity	97.0	100.0	98.5	100.0	100.0	99.3
Specificity	9.5	8.4	15.3	9.6	10.8	10.8
PPV	6.8	6.9	7.3	7	7.1	7
NPV	97.9	100.0	99.3	100.0	100.0	99.5
LR positive	1.1	1.1	1.2	1.1	1.1	1.1
LR negative	0.3	0	0.1	0	0	0.1
FPR	90.5	91.6	84.7	90.4	89.2	89.2
FNR	3	0	1.5	0	0	0.7

NOTE: Surveys were to screen patients with one or more HBV risk factor. Five-, six-, and seven-question models are based on model C. LR reports the number of times those who are HBV positive will have the risk factor for every one time those who are HBV negative will have the risk factor.

Abbreviations: CDC, Centers for Disease Control and Prevention; FPR, false-positive rate; HBV, hepatitis B virus; LR, likelihood ratio; MSM, men having sex with men; NPV, negative predictive value; PPV, positive predictive value.

An important finding of our study was that, regardless of the survey—CDC hepatitis risk assessment, modified CDC survey, or five- or six-question survey—approximately 90% of patients at our institution would answer affirmatively to at least one of the survey questions and would therefore require HBV serologic testing. Thus, even though we provided a brief, internally validated risk tool, our findings indicate that universal HBV screening is more efficient and practical. In populations in which the prevalence of risk factors is lower, the selective risk tool could be of benefit in that it could decrease the need for HBV testing to a lower proportion (< 90%) of patients; however, this hypothesis needs to be validated.

Our study has several limitations. It was conducted at a single academic cancer center, and the number of patients with HBV infection was small. We used bootstrapping, an internal validation approach, to validate our findings; thus, our models should be independently validated in large, multicenter, prospective studies. Owing to the low prevalence of chronic HBV infection in the United States, we were unable to develop separate models for chronic HBV infection and past HBV infection. Having separate models is important as the risk of HBV reactivation is higher for patients with chronic HBV infection than it is for patients with past HBV infection. We excluded patients who were previously tested or known to have HBV infection, which likely reduced the prevalence of HBV infection in our cohort. We included patients with HCC in our risk assessment, though all patients with HCC should be tested for HBV as part of standard medical practice. We did not ask participants about their HBV vaccination history. Because our study was conducted in the United States, our results are unlikely to be applicable to high-prevalence settings outside the United States. Our findings, though limited to patients with cancer who were awaiting anticancer therapy, may have relevance for the broader population of patients receiving immunosuppressive therapy for GI, rheumatologic, or dermatologic diseases.

In summary, our selective screening models on the basis of HBV risk factors and demographics performed as well as the 19-question modified CDC survey. A five-question HBV screening tool, with

questions about age, gender, race and ethnicity, birthplace, and household exposure to HBV infection, may be administered by medical assistants or self-administered by patients to identify patients who are at risk for HBV reactivation from anticancer therapy; however, our data indicated that the majority of our study population needed HBV testing despite the risk assessment tool if we aim for an FNR of zero, which reinforces the need for universal HBV screening. More efficient screening tools could be developed but would sacrifice sensitivity, leading to missed patients with HBV infection who are at risk for adverse liver outcomes and death as a result of reactivation. Future studies are needed to assess the cost effectiveness of universal testing compared with selective screening across populations who receive low-to-intermediate intensity anticancer regimens and with varying prevalence of HBV infection and range of FNR.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

- Weinbaum CM, Williams I, Mast EE, et al: Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 57:1-20, 2008
- American Association for the Study of Liver Diseases: AASLD practice guideline update: Chronic hepatitis B: Update 2009. www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf
- Reddy KR, Beavers KL, Hammond SP, et al: American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 148:215-219, quiz e16-e17, 2015 [Erratum: *Gastroenterology* 148:455, 2015]
- Hwang JP, Somerfield MR, Alston-Johnson DE, et al: Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. *J Clin Oncol* 33:2212-2220, 2015
- Baden LR, Swaminathan S, Angarone M, et al: Prevention and treatment of cancer-related infections, version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 14:882-913, 2016
- LeFevre ML; U.S. Preventive Services Task Force: Screening for hepatitis B virus infection in non-pregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 161:58-66, 2014
- National Comprehensive Cancer Network: Prevention and treatment of cancer-related infections (version 2.2014). http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
- Hwang JP, Fisch MJ, Zhang H, et al: Low rates of hepatitis B virus screening at the onset of chemotherapy. *J Oncol Pract* 8:e32-e39, 2012
- Day FL, Link E, Thursky K, et al: Current hepatitis B screening practices and clinical experience of reactivation in patients undergoing chemotherapy for solid tumors: a nationwide survey of medical oncologists. *J Oncol Pract* 7:141-147, 2011
- Hwang J, Suarez-Almazor ME, Cantor SB, et al: Impact of the timing of hepatitis B virus identification and anti-hepatitis B virus therapy initiation on the risk of adverse liver outcomes in patients receiving cancer therapy. *Cancer* 123:3367-3376, 2017
- Centers for Disease Control and Prevention: Hepatitis risk assessment. <https://www.cdc.gov/hepatitis/riskassessment/>
- Woolson RF, Clarke WR. *Statistical Methods for the Analysis of Biomedical Data*. New York, John Wiley and Sons, 2002 <https://doi.org/10.1002/9781118033050>
- Gonen M. *Analyzing Receiver Operating Characteristic Curves Using SAS*. Cary, NC, SAS Press, 2007
- Cameron AC, Trivedi PK. *Microeconomics Using Stata*. Stata Press, College Station, TX, 2009
- Spenatto N, Boulinguez S, Mularczyk M, et al: Hepatitis B screening: who to target? A French sexually transmitted infection clinic experience. *J Hepatol* 58:690-697, 2013
- Zurawska U, Hicks LK, Woo G, et al: Hepatitis B virus screening before chemotherapy for lymphoma: A

cost-effectiveness analysis. *J Clin Oncol* 30:3167-3173, 2012

17. Voican CS, Mir O, Loulergue P, et al: Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. *Ann Oncol* 27:2172-2184, 2016

18. Paul S, Saxena A, Terrin N, et al: Hepatitis B virus reactivation and prophylaxis during solid tumor

chemotherapy: A systematic review and meta-analysis. *Ann Intern Med* 164:30-40, 2016

19. Hwang JP, Fisch MJ, Lok AS, et al: Trends in hepatitis B virus screening at the onset of chemotherapy in a large US cancer center. *BMC Cancer* 13:534, 2013

20. Hsu PI, Lai KH, Cheng JS, et al: Prevention of acute exacerbation of chronic hepatitis B infection in

cancer patients receiving chemotherapy in a hepatitis B virus endemic area. *Hepatology* 62:387-396, 2015

21. Sanagawa A, Kuroda J, Shiota A, et al: Outcomes of the implementation of the computer-assisted HBView system for the prevention of hepatitis B virus reactivation in chemotherapy patients: A retrospective analysis. *J Pharm Health Care Sci* 1:29, 2015

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Models to Predict Hepatitis B Virus Infection Among Patients With Cancer Undergoing Systemic Anticancer Therapy: A Prospective Cohort Study

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